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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,333	OBERLEY ET AL.	
	Examiner	Art Unit	
	AMY H. BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-8,12-15,18-21 and 23-31* is/are pending in the application.

4a) Of the above claim(s) *5,23-26,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 3, 6-8, 12-15, and 18-21* is/are rejected.

7)☒ Claim(s) *27,30 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001 and 14 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 1/7/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/6/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2, 3, 5-8, 12-15, 18-21 and 23-31 are pending in the instant application. Claims 5, 23-26, 28 and 29 are withdrawn from consideration.

Applicant's amendments and/or arguments filed 1/7/08, with respect to the rejection(s) under 35 USC 102, have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, the following rejections are pending and in view of the amendments to the claims, a new grounds of rejection is applied as explained below.

Response to Claim Rejections - 35 USC § 112

Claims 8, 12-15, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of **breast cancer** using the claimed antisense oligonucleotides via **intratumoral injection**, does not reasonably provide enablement for treatment of any tumor using the claimed antisense oligonucleotides via any method of delivery. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, as explained in the office actions mailed on 8/24/06 and 9/6/07.

Applicant has cancelled claim 11, thereby obviating the rejection against this claim. Furthermore, the rejection is withdrawn against claim 27, as claim 27 is directed to an enabled embodiment of the invention.

It is noted that the instant rejection is maintained with respect to the breadth of the claims regarding recitation of treating any tumor type.

Applicant is enabled for a method of treating a **breast cancer** tumor in a mammal comprising administering via **intratumoral injection** to a mammal having the tumor a therapeutically effective amount of the claimed antisense nucleic acids.

Although applicant asserts that the claims are supported by a number of working examples, the only *in vivo* working example disclosed in the instant specification is that of treating breast cancer tumors with the instant oligonucleotide via xenografts delivered via intratumoral injection, which is not commensurate in scope with the instantly recited claims directed to treating any tumor type and/or via any mode of administration.

The teachings of the specification regarding treating other tumor types, such as melanoma and glioma are *in vitro* examples and are therefore not commensurate in scope with the instant claims which recite “a method of treating a tumor in a mammal”.

The specification describes prophetic methods of treatment using antisense oligos targeted to human manganese superoxide dismutase, and further exemplifies method of using the claimed composition to inhibit the expression of human manganese

superoxide dismutase in a mouse xenograft injected with MCF-7 cells, which had the effect of inhibiting tumor growth in said model.

Applicant asserts that Church et al. cannot indicate unpredictability in practicing the instant invention because the tumor cells of Church et al. have little steady-state MnSOD expression. Contrary to applicant's assertion, the method and molecules utilized by Church et al. do not need to be identical to the instant method and molecules. Church et al. teach that increasing manganese superoxide dismutase expression actually suppresses the malignant phenotype of human melanoma cells. This runs contrary to the underlying principle of the instantly claimed invention, whereby inhibition of the same target is claimed to suppress the malignant phenotype in humans. Regardless of the specific molecules used or the steady-state level of MnSOD expression, Church et al. increased the expression of manganese superoxide dismutase and got a result that is contrary to the instant principle. Accordingly, the claimed invention cannot work over its entire breadth, since the combination of the specification and the prior art teach suppression of malignancy resulting from both increasing and decreasing the expression of the instantly recited target. Although applicant asserts that the amount of experimentation needed is not undue, the examples in the instant specification regarding tumor types other than breast cancer are *in vitro* and are not necessarily predictable of *in vivo* activity. Church et al. is additional evidence that suggests that inhibition of the identical target would have the opposite effect in at least one other cancer type, further supporting the unpredictability of the instant breadth.

It is noted that the disclosure is required to be enabled over the instant scope at the time of filing:

MPEP 2164.01
Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)
A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of the antisense oligonucleotide *in vivo* via intratumoral injection would result in treatment of such a broad scope of tumor types.

In conclusion, applicant is enabled for a method of treating a **breast cancer** tumor in a mammal comprising administering via **intratumoral injection** to a mammal having the tumor a therapeutically effective amount of the claimed antisense nucleic acids.

Claim Objections

Claims 27, 30 and 31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is directed to an antisense nucleic acid that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein “the sequence” is SEQ ID NO: 2. However, neither of the nucleic acids of the claim are referred to as a “sequence” and therefore there is insufficient antecedent basis for this limitation in the claim. Claim 21 is rejected to because it depends from claim 20. Recitation in claim 20 of "An antisense nucleic acid sequence that specifically binds to a nucleic acid encoding an antioxidant enzyme start codon, wherein the sequence is SEQ ID NO: 2", for example, would obviate this rejection.

As currently recited, it is unclear which nucleic acid the sequence is referring to and thus the claims are indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 6 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Huang et al. (WO 02/03979 A2).

The instant claims are directed to an antisense nucleic acid that is about 18 to 26 nucleotides in length, wherein the entire antisense nucleic acid is at least 90% complementary or is 100% complementary to and binds specifically to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase and wherein the contiguous portion includes the start codon of the nucleic acid encoding the manganese superoxide dismutase. The antisense nucleic acid is about 20 nucleotides in length.

Huang et al. teach an antisense oligonucleotide that is 25 nucleotides in length, meeting the instant limitation of "about 18 to 26" or "about 20" nucleotides in length. The antisense oligonucleotide of Huang et al. comprises instant SEQ ID NO: 2 and is 100% complementary to a nucleic acid encoding a human manganese superoxide dismutase (instant SEQ ID NO: 11) including the start codon (see SEQ ID NO: 2 on page 6 of Huang et al., as well as search result #4 in SCORE search results titled "20080320_143124_us-09-993-333-11.sl.rng").

Therefore, the instant claims are anticipated by Huang et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 3, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (WO 02/03979 A2), in view of Baracchini et al. (US 5,801,154).

The instant claims are directed to an antisense nucleic acid that is about 18 to 26 nucleotides in length, wherein the entire antisense nucleic acid is at least 90% complementary or is 100% complementary to and binds specifically to a contiguous portion of a nucleic acid that encodes a human manganese superoxide dismutase and wherein the contiguous portion includes the start codon of the nucleic acid encoding the manganese superoxide dismutase. The antisense nucleic acid is about 20 nucleotides in length and is phosphorothiolated.

Huang et al. teach an antisense oligonucleotide that is 25 nucleotides in length, meeting the instant limitation of "about 18 to 26" or "about 20" nucleotides in length.

The antisense oligonucleotide of Huang et al. comprises instant SEQ ID NO: 2 and is 100% complementary to a nucleic acid encoding a human manganese superoxide dismutase (instant SEQ ID NO: 11) including the start codon (see SEQ ID NO: 2 on page 6 of Huang et al., as well as search result #4 in SCORE search results titled "20080320_143124_us-09-993-333-11.sl.rng").

Huang et al. do not teach phosphorothioate modifications.

Baracchini et al. teach that phosphorothioate modifications enhance antisense oligonucleotide resistance to nuclease digestion.

It would have been obvious to phosphorothiolate the antisense oligonucleotide of Huang et al.

One would have been motivated to incorporate phosphorothioate modifications into the antisense nucleic acid of Huang et al. because Baracchini et al. teaches that these modifications enhance antisense oligonucleotide resistance to nuclease activity.

One would have a reasonable expectation that the modification of Baracchini et al. would add the same benefit of enhancing resistance to nucleases to the antisense nucleic acid of Huang et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY H. BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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